

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: ) Examiner: Basi, Nirmal Singh  
Avi ASHKENAZI, *et al.* )  
Application Serial No. 09/903,520 ) Art Unit: 1646  
Filed: July 11, 2001 ) Confirmation No: 1093  
For: **SECRETED AND TRANSMEMBRANE** ) Attorney's Docket No. 39780-1618 P2C46  
**POLYPEPTIDES AND NUCLEIC ACIDS** )  
**ENCODING SAME** )  
**Customer No. 35489**  
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**FILED VIA EFS**

December 3, 2007

**ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES**  
**APPELLANTS' BRIEF**

**MAIL STOP APPEAL BRIEF - PATENTS**

Commissioner for Patents -  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Dear Sir:

On February 22, 2007, the Examiner made a Final rejection to pending Claims 39-47 and 49-51. A response and Notice of Appeal was filed on August 2, 2007.

Appellants hereby appeal to the Board of Patent Appeals and Interferences from the last decision of the Examiner. This Brief is timely filed requesting a **two-month extension of time** with fees.

The following constitutes Appellants' Brief on Appeal.

**1. REAL PARTY IN INTEREST**

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Patent Application Serial No. 09/665,350 recorded July 9, 2001, at Reel 011964 and Frame 0181.

**2. RELATED APPEALS AND INTERFERENCES**

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO335." There exist two related patent applications: 1) U.S. Patent Application Serial No. 09/904,786, filed July 12, 2001 (containing claims directed to PRO335 antibodies), and 2) U.S. Patent Application Serial No. 09/909,088, filed July 18, 2001 (containing claims directed to polynucleotides encoding PRO335 polypeptides). These applications are also under final rejection from the same Examiner and are based upon the same type of outstanding rejections, and so appeals are being pursued independently and concurrently herewith.

**3. STATUS OF CLAIMS**

Claims 1-38 and 48 were canceled without prejudice or disclaimer. Claims 39-47 and 49-51 stand rejected in this application. Appellants appeal the rejection of the pending claims.

A copy of the rejected claims involved in the present Appeal is provided in Section VIII.

**4. STATUS OF AMENDMENTS**

No amendments to claims were submitted after the final rejection. All previous amendments have been entered.

**5. SUMMARY OF CLAIMED SUBJECT MATTER**

The invention claimed in the present application is related to an isolated polypeptide comprising the amino acid sequence of the polypeptide of SEQ ID NO:290 referred to in the present application as "PRO335"; the amino acid sequence of the polypeptide of SEQ ID NO:290, lacking its associated signal peptide; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927 (Independent Claim 44 and Claims 45-47 and 49). The invention is further directed to polypeptides having at least 80% (independent Claim 39), 85% (independent Claim 40), 90% (independent Claim 41), 95% (independent Claim 42), or 99% (independent Claim

43) amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:290; the amino acid sequence of the polypeptide of SEQ ID NO:290, lacking its associated signal peptide; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927, wherein said polypeptide is an immunostimulant. PRO polypeptide variants (independent claims 39-43) are described in the specification at, for example, page 57, lines 2-14 and page 112, line 37 onwards, while identities to PRO polypeptide are described in the specification at, for example, page 67, line 34 onwards to page 69.

The preparation of chimeric PRO polypeptides (Independent Claim 50 and claim 51), including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin, is set forth in the specification at page 74, lines 23 to page 75, line 5. Examples 53-56, pages 192-199, describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells.

The PRO335 polypeptide was shown to induce proliferation of stimulated T-lymphocytes in a mixed lymphocyte reaction as compared to controls (Example 74), which provides support for all claimed independent claims. PRO335 is also described as a polypeptide having homology to proteins of the leucine rich repeat superfamily, and particularly, are related to LIG-1 (page 30, line 11, to page 31, line 18, and page 110, lines 26-36). The full-length PRO335 polypeptide having the amino acid sequence of SEQ ID NO:290 is described in the specification at, for example, page 50-51, lines 1-22, in Figure 102 and in SEQ ID NO:290. Page 63, lines 34-37 of the specification provides the description for Figures 101 and 102.

Example 74 (page 208) shows that PRO335 tested positive in the mixed lymphocyte reaction (MLR) assay, demonstrating that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes, and therefore would have utility in the treatment of conditions where the enhancement of an immune response would be beneficial. In addition, Example 77 shows the ability of PRO335 to stimulate an immune response and induce inflammation at the site of injection in the skin vascular permeability assay, using the hairless guinea pig injected with the Evans blue dye as a model system.

## **6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

I. Whether the data generated in the MLR assay (Example 74) satisfies the utility requirement set forth in 35 U.S.C. § 101, and further, whether the data satisfies the enablement requirement set forth in 35 U.S.C. § 112, first paragraph, for the invention claimed in Claims 39-47 and 49-51.

II. Whether the data generated in the MLR assay (Example 74) satisfies the Enablement requirement set forth in 35 U.S.C. § 112, first paragraph, for the invention claimed in Claims 39-47 and 49-51.

III. Whether the data generated in the MLR assay (Example 74) satisfies the Written Description requirement set forth in 35 U.S.C. § 112, first paragraph, for the invention claimed in Claims 39-47 and 49-51.

## **7. ARGUMENT**

Summary of the Arguments:

### **Issue I: Utility/ Enablement**

Appellants submit that patentable utility for the PRO335 polypeptide is based upon data derived from the mixed leukocyte reaction (MLR) assay. The MLR assay is a well-established and accepted assay in the art for evaluating test compounds for their ability to stimulate T-lymphocyte proliferation *in vitro*. Example 74 of the instant specification shows that PRO335 tested positive in the mixed lymphocyte reaction (MLR) assay, demonstrating that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes, and therefore has utility in the treatment of conditions where the enhancement of an immune response would be beneficial, like to treat tumor progression/ regression in cancer. In fact, the Examiner himself acknowledges that MLR is an art accepted assay for identifying immunomodulatory compounds at least on page 3 and on page 10, paragraph 2, line 8 of the Final Office Action mailed February 22, 2007. Appellants have submitted several references throughout the prosecution of this case that supports the Appellants' position that the *in vitro* MLR assay has been successfully used to identify compounds having immunomodulatory activity *in vivo*, which the Examiner has acknowledged. By the priority date of the present application (September 17, 1998), it was well known that stimulators of T-cell proliferation would have utility in fighting diseases like: viral

infections, including retroviral infections, (HIV infection or Epstein-Barr infection), or in the treatment of invasive cancers such as melanoma.

Appellants also note that the claimed polypeptide variants having at least 80-99% sequence identity to the polypeptide sequence of SEQ ID NO:290, which recite the functional recitation "wherein said polypeptide is an immunostimulant," have utility based on the MLR assay. Thus, each claimed variant shares an immunostimulant property besides having sequence identity to the PRO335 polypeptide. The specification provides ample guidance to the skilled artisan to identify variant polypeptide sequences and includes a detailed protocol of the MLR assay.

In addition, Appellants submitted with their Preliminary Amendment of October 25, 2004, a Declaration by Dr. Sherman Fong, who is an unquestionable expert in the field. The Declaration provides several examples of important clinical applications for immune stimulants which have shown activity in a mixed lymphocyte reaction assay, such as the chemokine IL-12, which finds utility in the treatment of melanoma due to its ability to stimulate immune response. Dr. Fong's declaration states that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant." The specification discloses that PRO335 has an activity of at least 180% of the control (see Example 74 of the instant specification).

Despite Dr. Fong's unequivocal statement, and the Examiner's acknowledgement that "the MLR assay is an accepted *in vitro* model for screening immunosuppressive agents for use in the prevention of graft-versus-host disease and graft rejection" (see page 14, second paragraph of the Final Office action of February 22, 2007), and the teachings of the present specification, the Examiner has asserted that "this biological activity does not correlate to use of the claimed nucleic acid in a therapeutically effective manner, as the asserted use of the claimed invention proposes." The Examiner adds that "the specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay." The Examiner also takes issue with Dr. Fong's declaration and does not find it persuasive allegedly because "the expert has interest in the outcome of the case since (he)

is listed as an inventor and is employed by the assignee.” The Examiner questions the significance of the expert’s conclusions based on alleged lack of use of proper controls. The Examiner erroneously concludes that undue experimentation would be need to practice the invention.

Appellants respectfully submit that, despite the Examiner’s acknowledgment of PRO335 as an immunosuppressive molecule based on a positive MLR assay, the Examiner’s general concern here seems to be with a requirement for statistical results, demonstration of controls, and the underlying therapeutic mechanism for its effectiveness, and not with the positive result itself. Appellants respectfully submit that the Examiner’s concern is not a proper basis for a utility rejection. The Examiner seems to apply a standard that might be appropriate if the issue at hand were the **regulatory approval of a drug** based on the immunoenhancer activity of PRO335, but is **fully inappropriate for determining whether the “utility” standard of the Patent Statute is met.** The FDA, in reviewing an application for a new immunoenhancer drug, will indeed ask for actual numerical data, statistical analysis, therapeutic effectiveness and other specific information, before the drug is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval.

Moreover, the evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant.

The Examiner has not shown that a lack of correlation typically exists between the results of the MLR assay in this instance and use of an immunomodulator such as PRO335 in a therapeutically effective manner. In fact, Appellants submit that the teachings within Picotti *et al.* and Campo *et al.* discussed during prosecution, support the Appellants' position that the *in vitro* MLR assay can and has been successfully used to identify compounds having immunomodulatory activity *in vivo*. Appellants add that the Examiner has misinterpreted the specification, which clearly states what controls were used in the instant case, as will be elaborated upon below. In fact, based on such teachings, one of ordinary skill in the art would

find it 'more likely than not' for molecules testing positive in the disclosed MLR assay, like PRO335, to have real-world therapeutic utility as immunostimulants *in vivo*; and would also know exactly how to use the claimed PRO335 polypeptides, to treat disease conditions that are well-known and studied in the art: for example, in the treatment of viral infections and cancer, without any undue experimentation. Thus the Patent Office has failed to meet its initial burden of proof that Appellants' claims of utility are not substantial or credible.

Therefore, Appellants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed PRO335 polypeptides, since PRO335 is useful as an immunostimulant. In view of the teachings of the instant specification and the knowledge in the art, one of ordinary skill in the art would understand exactly how to use the recited polypeptides to treat a variety of diseases like viral infections, or cancer, diseases, where immunostimulation is known to be therapeutic, without any undue experimentation.

### **Issue II: Enablement**

Regarding the enablement rejection, Appellants note that the specification provides ample guidance to allow the skilled artisan to make and use those variant PRO335 polypeptides that are useful in the treatment of conditions like viral infections or cancer, and further, one skilled in the art would know how to use these polypeptides without any undue experimentation.

Accordingly, Appellants submit that the instant specification and the MLR assay suffices to provide enablement for the claimed subject matter, without any undue experimentation.

### **Issue III: Written Description**

Regarding the written description rejection, Appellants note that the specification provides ample guidance to allow the skilled artisan to identify those polypeptides with 80-99% identity to the polypeptide defined in SEQ ID NO.: 290. Further, the Appellants have provided a well-accepted *in vitro* MLR assay can and has been successfully used to identify compounds having immunomodulatory activity *in vivo* (Example 74). Moreover, the instant invention evidences the actual reduction to practice of full-length PRO335 of SEQ ID NO:290, with or without its signal sequence, or encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927. Therefore, the claimed polypeptides are defined both by functional as well as structural features and is therefore limited. In fact, this

would not encompass combinations larger than  $10^{23}$  and  $10^{56}$  as the Examiner contends. Therefore, the Examiner's contention is not appropriate. Accordingly, Appellants submit that the instant specification and the MLR assay meet the written description standards set by the U.S.P.T.O. for the claimed subject matter.

These arguments are all discussed in further detail below under the appropriate headings.

Detailed Arguments:

**ISSUE I: The Data Generated in the MLR Assay Satisfies the Utility/ Enablement Requirement of 35 U.S.C. §§101/112, First Paragraph for Claims 39-47 and 49-51**

Appellants submit that the results of the MLR assay in the instant specification (and in the priority U.S. Provisional Patent Application Serial No. 60/100,858) provides at least one credible, substantial and specific asserted utility for the claimed PRO335 polypeptides under 35 U.S.C. §§101/112, first paragraph.

**A. Legal Standard for Utility**

According to 35 U.S.C. §101:

Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.  
(Emphasis added).

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In. explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations

used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a “substantial” utility.” (M.P.E.P. §2107.01, Emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II(B)(1) gives the following instruction to patent examiners: “If the Applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, the Utility Guidelines restate the Patent Office’s long established position that any asserted utility has to be “credible.” “Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record ... that is probative of the applicant’s assertions.” (M.P.E.P. §2107 II(B)(1)(ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The case law has clearly established that Applicant’s statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.<sup>1</sup> The PTO has the initial burden to prove that Applicant’s claims of usefulness are not believable on their face.<sup>2</sup> In general, an Applicant’s assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, “unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.”<sup>3,4</sup>

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<sup>1</sup> *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

<sup>2</sup> *Ibid.*

<sup>3</sup> *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

<sup>4</sup> See also *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

The well established case law is clearly reflected in the Utility Examination Guidelines (“Utility Guidelines”),<sup>5</sup> which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted “specific, substantial, and credible utility” or a “well-established utility.” Under the Utility Guidelines, a utility is “specific” when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the “substantial utility” standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an Applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a ‘substantial’ utility.”<sup>6</sup> Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,<sup>7</sup> gives the following instruction to patent examiners: “If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Appellants note that the phrase cited above “useful for any practical purpose” merely requires that an invention be useful, and does not require that it be *better* than other competing subject matter: “The Federal Circuit stated that a finding that “an invention that is an ‘improvement’ is not a prerequisite to patentability” since it “is possible for an invention to be less effective than existing devices but nevertheless meet the statutory criteria for patentability.” (*Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*)<sup>8</sup>

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<sup>5</sup> 66 Fed. Reg. 1092 (2001).

<sup>6</sup> M.P.E.P. §2107.01.

<sup>7</sup> M.P.E.P. §2107 II(B)(1).

<sup>8</sup> *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 1 USPQ2d 1196 (Fed. Cir. 1986).

In interpreting the utility requirement, in *Brenner v. Manson*,<sup>9</sup> the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent Applicant disclose a "substantial utility" for his or her invention, *i.e.*, a utility "where specific benefit exists in currently available form."<sup>10</sup> The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."<sup>11</sup>

Later, in *Nelson v. Bowler*,<sup>12</sup> the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The Court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."<sup>13</sup>

Moreover, in *Cross v. Iizuka*,<sup>14</sup> the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.*, there is a reasonable correlation there between."<sup>15</sup> The Court perceived, "No insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."<sup>16</sup>

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<sup>9</sup> *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

<sup>10</sup> *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

<sup>11</sup> *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

<sup>12</sup> *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

<sup>13</sup> *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

<sup>14</sup> *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

<sup>15</sup> *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

<sup>16</sup> *Id.*

Furthermore, M.P.E.P. §2107.03 (III) states that:

"If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

Thus, the legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described.

Compliance with 35 U.S.C. §101 is a question of fact.<sup>17</sup> The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.<sup>18</sup> Accordingly, Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. With respect to asserted therapeutic utilities based upon *in vitro* data, an Applicant "does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty."<sup>19</sup> The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. The issue will then be decided on the totality of evidence.

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<sup>17</sup> *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 US 835 (1984).

<sup>18</sup> *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

<sup>19</sup> M.P.E.P. §2107.03.

## **B. Proper Application of the Legal Standard**

Appellants submit that the results of the mixed lymphocyte reaction (MLR) assay described in Example 74 of the instant specification (and in the priority U.S. Provisional Patent Application Serial No. 60/100,858) provides at least one credible, substantial and specific asserted utility for the claimed PRO335 polypeptides under 35 U.S.C. §§101/112, first paragraph. The positive result for PRO335 in the MLR assay described in Example 74, at page 208 of the specification demonstrates that, PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes.

The MLR was a well-established assay at the priority date of the present application (September 17, 1998) for evaluating test compounds, such as the PRO335 polypeptide, for their ability to stimulate T-lymphocyte proliferation *in vitro*, and consequently, for assessing the immune response of an individual. The MLR assay is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc. (1991) which is referenced in Example 74, the entire content of which is expressly incorporated by reference into the disclosure of the present application (see page 147, line 16-17). In brief, in this method, an immune response results upon mixing T-cells from antigenically distinct individuals under cell culture conditions. An MLR reaction can be monitored quantitatively by, for example, following the incorporation of tritiated thymidine during DNA synthesis, or by observing blast formation, or by other methods well known in the art.

According to the specification, positive increases over control in this assay are considered to be positive results, with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein. PRO335 (SEQ ID NO: 290) tested positive in this assay, using the described criteria. Example 74 further explains that compounds which stimulate proliferation of lymphocytes in this assay "are useful therapeutically where enhancement of an immune response is beneficial." Accordingly, PRO335 has utility in the treatment of conditions where the stimulation of lymphocyte proliferation would be desirable, like to treat tumor progression/ regression in cancer.

In further support of utility based upon the MLR assay, Appellants have submitted (with their Response filed October 25, 2004) the Declaration of Sherman Fong, Ph.D. Dr. Fong is an inventor of the above-identified patent application, and an experienced scientist familiar with the MLR assay, which was used by him and others under his supervision, to test the immune stimulatory or immune inhibitory activity of novel polypeptides discovered in Genentech's Secreted Protein Discovery Initiative project, including PRO335. The Fong Declaration explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. Dr. Fong proceeds to explain (paragraph 7 of the Declaration) that dendritic cells are potent antigen-presenting cells that are able to "prime native T-cells *in vivo*." Once activated by dendritic cells, the T-cells are capable of interacting with other antigen-presenting cells (B cells and macrophages) to produce additional immune responses from these cells.

As Dr. Fong states, "the MLR assay of the present application is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR, and thus identifies immune stimulants that can boost the immune system to respond to a particular antigen that may not have been immunologically active previously" (Paragraph 8 of the Fong Declaration). Dr. Fong also emphasizes that, immunostimulants are important and highly desirable in the treatment of cancer and in enhancing the effectiveness of previously identified treatments for cancer. Supportive evidence for this teaching comes from the art such as Steinman *et al.* (submitted as Exhibit B with the Amendment filed October 25, 2004) who state that "**...medicine needs therapies that enhance immunity or resistance to infections and tumors**" (page 1, column 1, line 7; emphasis added).

In paragraph 9 of his Declaration, Dr. Fong provides examples of important clinical applications for immune stimulants which have been shown to stimulate T-cell proliferation in the MLR assay. As Dr. Fong explains,

"IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay [Gubler *et al.* PNAS 88, 4143 (1991) (Exhibit C)]. IL-12 was first identified in just such an MLR. In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of the approach, relying on the immune

stimulatory activity of IL-12, for the treatment of melanoma. [Peterson *et al.* Journal of Clinical Oncology 21 (12). 2342-48 (2003) (Exhibit D)] They extracted circulating white blood cells carrying one or more markers of melanoma cells, isolated the antigen, and returned them to the patients. Normally patients would not have an immune response to his or her own human antigens. The patients were then treated with different doses of IL-12, an immune stimulant capable of inducing the proliferation of T-cells that have been co-stimulated by dendritic cells. Due to the immune stimulatory effect of IL-12, the treatment provided superior results in comparison to earlier work, where patients' own dendritic cells were prepared from peripheral blood mononuclear cells (PBMCs), treated with antigens, then cultured *in vitro* and returned to the patient to stimulate anti-cancer response. [Thurner *et al.* J. Exp. Med. 190 (11), 1669-78 (1999) (Exhibit E)]."

Therefore, the art, as exemplified by Gubler *et al.* and Thurner *et al.*, in fact supports the Appellants' position that an MLR result is useful for identifying compounds with immunomodulatory activity *in vivo*. Dr. Fong concludes that (paragraph 10):

It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant."

Accordingly, the positive results obtained in this assay clearly establish the immunostimulant utility for the PRO335 polypeptides claimed in the present application, and the specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose.

### **C. A prima facie case of lack of utility has not been established**

As a preliminary matter, Appellants submit that, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility.

With respect to asserted **therapeutic utilities** based upon *in vitro* data, an applicant "does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty" (M.P.E.P. §2107.03.). The law

requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Appellants have asserted, and the Examiner himself has acknowledged that the instant MLR assay is useful to identify compounds having immuno-modulatory activity *in vivo*. Accordingly, PRO335 would be useful to enhance immunostimulation in certain disease conditions such as cancer. Based on the well-published literature in the art, one skilled in the art would accept this assertion from the Applicant as credible and substantial.

Yet, the Examiner adds that the specification does not provide any values or data for the proteins tested in the assay, nor any statistical values measured in the assay.

Appellants respectfully submit that, the Examiner's general concern here seems to be with a requirement for statistical results, demonstration of controls, and the underlying therapeutic mechanism for its effectiveness, and not with the positive result itself. Appellants respectfully submit that the Examiner's concern is not a proper basis for a utility rejection. The Examiner seems to apply a standard that might be appropriate if the issue at hand were the **regulatory approval of a drug** based on the immunoenhancer activity of PRO335, but is **fully inappropriate for determining whether the "utility" standard of the Patent Statute is met**. The FDA, in reviewing an application for a new immunoenhancer drug, will indeed ask for actual numerical data, statistical analysis, therapeutic effectiveness and other specific information, before the drug is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to utility for an immunostimulant as well. The identification of an immunostimulatory utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Furthermore, the mechanism of action need not be understood for attaining that utility. In fact, as stated by the Federal Circuit, “it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works.” *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that “[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: “[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for finding lack of utility.” *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753,762, 221 USPQ 473,480 (Fed. Cir. 1984).” Thus, Appellants submit that such a concern is misplaced, and cannot properly form the basis of the rejections of the present claims.

Moreover, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant.

The Examiner has not shown that a lack of correlation typically exists between the results of the MLR assay in this instance, and use of an immunomodulator such as PRO335 in a therapeutically effective manner. In fact, Appellants submit that the teachings within Picotti *et al.*, Campo *et al.* discussed during prosecution, support the Appellants' position that the *in vitro* MLR assay can and has been successfully used to identify compounds having immuno-modulatory activity *in vivo*.

Accordingly, Appellants respectfully submit that the Examiner's comments fail to support a *prima facie* case of lack of utility.

**D. The Fong Declaration supports "real world" utility for proteins that test positive in the MLR assay**

The Examiner also takes issue with Dr. Fong's declaration and does not find it persuasive allegedly because “the expert has interest in the outcome of the case since (he) is listed as an inventor and is employed by the assignee.” The Examiner questions the significance of the expert's conclusions based on alleged lack of use of proper controls. The Examiner erroneously concludes that undue experimentation would be need to practice the invention.

Appellants respectfully submit that Dr. Fong's statements are made under oath, and are asserted based on his vast knowledge and experience in the use and interpretation of the MLR assay. Furthermore, The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.<sup>20</sup> "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"<sup>21</sup> Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner"<sup>22</sup>. Appellants also respectfully draw the Examiner's attention to the Utility Examination Guidelines<sup>23</sup> which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Fong Declaration) states that "(i)t is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant." Therefore, barring evidence to the contrary regarding the above statement in the Fong Declaration, this rejection is improper under both the case law and the Utility guidelines.

The Examiner also mistakenly contends on page 15 of the Final Office Action (line 1) that "no 'particular antigen' is identified in the specification; there is no guidance as to how PRO335 could be used to boost the response to any antigen".

As Appellants have submitted previously, the PRO335 molecule, just like other immunostimulants (e.g., cytokines), stimulates cellular responses (cellular immunity) rather than

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<sup>20</sup> *In re Rinehart*, 531 F.2d 1084, 189 U.S.P.Q. 143 (C.C.P.A. 1976) and *In re Piasecki*, 745 F.2d. 1015, 226 U.S.P.Q. 881 (Fed. Cir. 1985).

<sup>21</sup> *In re Alton*, 37 U.S.P.Q.2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)).

<sup>22</sup> *In re Alton*, *supra*.

<sup>23</sup> Part IIB, 66 Fed. Reg. 1098 (2001).

humoral responses. Therefore, no "particular antigen" in the immune system need be identified. Therefore, this rejection is improper.

It was well known in the art at the time of filing of the instant application that T-cells are highly important in the body's natural defense mechanisms for fighting infections. For example, viral infections, such as HIV infection, were well known to result of a reduced T cell count. It was also well known at the time of filing that T cells could recognize tumor antigens and kill tumors. Therefore, one skilled in the art would reasonably know how to use the PRO335 immunostimulant, for instance, to boost the body's natural defense mechanisms for fighting infections or to recognize tumor antigens and/or to reduce and/or kill tumors.

The Examiner's misunderstanding of the instant MLR assay is further demonstrated in the Examiner's discussion of "controls" (see page 15 of the Final Office Action mailed February 22, 2007). The Examiner has asserted that "Current Protocols in Immunology" in fact describes many variables that must be controlled for. The Examiner alleges that in the instant application, no such controls such as for maximum response or for the inherent variability of individual responses are provided, no indication of the statistical significance of the result, no autologous controls, without giving any valid reason for doubting or questioning the assay controls used in the instant invention (emphasis added).

First of all, Appellants submit that these controls are only needed when the purpose of carrying out the MLR assay is to evaluate the properties of the stimulator cells. The comparisons to mismatched (maximum response) and autologous (background) controls allow one to determine the degree of HLA class II antigen similarity between the stimulator cells and the responder cells. Such determinations, however, are not relevant to the MLR assay of Example 74.

Appellants add that the MLR assay described in the instant specification is a comparative one (increases of greater than or equal to 180% is preferred), meaning that the utility is based upon a comparison of relative expression levels between a known polypeptide and an unknown PRO molecule. Additionally, Appellants expressly assert that the observed difference for PRO335 is significant as discussed in Example 74 of the instant specification. Therefore, contrary to the Examiner's position, controls were discussed in the specification. Further, regarding the Examiner requiring certain types of controls in the assay, again, Appellants submit

that the Examiner appears to have misinterpreted the intent of the controls in the MLR assay throughout this rejection. For instance, the mixing of the stimulator and responder cells in the instant MLR is expected to lead to T cell proliferation even in the absence of any test protein. The point of the MLR assay is to measure the extent to which the test protein can enhance the expected proliferation of the stimulated T cells. Appellants submit that the controls mentioned by the Examiner are only needed when the purpose of carrying out the MLR assay is to evaluate the properties of the stimulator cells. On the other hand, the purpose of the instant MLR assay, as discussed above, is to characterize test proteins such as PRO335, not stimulator cells. So, the precise extent to which the stimulator cells stimulate the responder cells is not significant; instead, what matters is the degree to which the test protein increases this response. The extent to which the test protein increases the response of the T cells is measured by comparison to a negative control reaction, which uses either cell culture medium, or a non immunostimulant molecule, CD4-IgG, as a negative control. Because the response in the test reaction is compared to a negative control reaction, and because both reactions use the same stimulator and responder cells at the same time, additional controls to determine the precise properties of these cells are not required.

Therefore, Appellants maintain that the assay controls used in the instant invention were appropriate, as discussed in clear detail in the Fong Declaration and throughout prosecution, and thus, the data for PRO335 in Example 74 (MLR assay) would be considered as meaningful, by one skilled in the art.

Appellants add that references Gubler *et al.* and Peterson *et al.* that were previously submitted, were not submitted to show MLR activities of PRO335 (which is novel), but to show that other investigators used similar MLR assays to the one described in the instant specification, to conclude that their molecules stimulate T-cell proliferation and can be useful to enhance immune response. Appellants maintain their position regarding references Gubler *et al.* and Peterson *et al.*

Accordingly, Appellants respectfully submit that the Examiner's comments fail to support a *prima facie* case of lack of utility.

*The art in fact supports the Appellants' position that an MLR result is useful for identifying compounds with immunomodulatory activity in vivo*

Appellants submit that the references Picotti *et al.* and Campo *et al.* study allograft rejections and immunosuppression of graft rejection using test compounds *in vitro*. These references, in combination with others cited by Appellants, demonstrate that the art as a whole recognizes that the mixed lymphocyte reaction (MLR) is in fact a widely used *in vitro* assay for identifying immunomodulatory compounds.

For example, Picotti *et al.* confirm that "IL-12 is also a key cytokine involved in promoting cell mediated immune responses *in vivo*" (page 1459, col. 1). Thus, the fact that a molecule such as IL-12, which is a known immunostimulant *in vivo*, does not accelerate graft rejection supports Appellants' argument that graft rejection is a specific pathway that does not necessarily reflect general immunoregulatory function. Picotti *et al.* too draw a similar conclusion, suggesting that "the magnitude of Th1-driven alloimmune response may not correlate directly to the severity of graft rejection," perhaps because Th2-driven immune responses are more relevant to graft rejection (page 1459, col. 2). Therefore, Picotti *et al.*, provides evidence that a molecule which does not show *in vivo* activity in a specific graft versus host interactive pathway may still have general immunomodulatory activity.

Campo *et al.* set out to look for an inhibitor of MHC *in vitro* which would have the fewest side effects *in vivo* (see Abstract). The authors note that high concentrations of zinc "impair **all** T cell and monocyte function" (page 20; emphasis added). The authors took this impairment as an indicator of toxicity, and therefore intentionally used concentrations of zinc below that at which all T-cell function was impaired, in order to identify a concentration range that would not result in toxic effects. However, that does not mean that Campo *et al.* found zinc to have no immuno-suppressive activity *in vivo*. In fact, the authors conclude, based upon their MLC results, that "zinc **could become an immunosuppressant in transplantation medicine without toxic side effects**" (page 21; emphasis added). Thus Campo *et al.* supports Appellants' position that those of skill in the art would interpret the results of MLC assays as having physiological relevance.

In fact, Appellants note that the authors stated that the MLR is an important method with a good predictive value. For example, Campo *et al.* teach that "the human mixed lymphocyte

culture (MLC) is an important method to test donor-recipient compatibility in bone marrow transplantation. It could be shown that cytokine release, especially IFN- $\gamma$ , **has a very good predictive value with regard to the transplantation outcome**, as cytokines play a major role in the generation of an alloreactive immune response and for the induction of graft rejection *in vivo*.....Landolfo *et al.* inhibited T-cell reactivity by the addition of anti-IFN- $\gamma$  **both *in vitro* and *in vivo***" (see page 18; emphasis added). Further, Picotti *et al.* showed that the IL-12R $\beta$ 1 subunit was critical for IL-12 driven enhanced alloimmune response *in vitro* and *in vivo* (see abstract). Thus, while there are instances of unpredictability using the MLR assay, there are many studies showing predictable results, including studies from Picotti, Landolfo and the IFN- $\gamma$  study. Finally, Campo *et al.* teaches that "cyclosporin A, FK506, and other substances are used to prevent graft rejection. **In vitro experiments revealed an inhibition of the MLC**" (page 16). Thus the teachings of Campo *et al.* confirm that inhibition of the MLR is observed for known immunoinhibitory molecules, that are in actual clinical use.

Thus, in fact, references Picotti *et al.* and Campo *et al.* support the Appellants' position that it is more likely than not that the *in vitro* MLR assay can be successfully used to identify compounds having immunomodulatory activity *in vivo*.

**E. One Skilled in the Art would know how to make and use the variant proteins without undue experimentation based on the teachings in the art and in the specification**

The fact remains that the results of the MLR assay were positive, indicating that PRO335 is an immunostimulant. The Examiner's concern that the results require undue experimentation further, do not negate the positive results of the assay, that is, that PRO335 is a an immunostimulant molecule. As discussed above, one of ordinary skill in the art in possession of these results would, more likely than not, acknowledge that the PRO335 polypeptides are useful as an immunostimulant agents. Moreover, as the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."<sup>24</sup> As discussed above, a considerable amount of experimentation is permissible, if it is merely routine.

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<sup>24</sup> M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

In view of the above, Appellants submit that a valid case for utility has been made and would be considered credible by a person of ordinary skill in the art. Indeed, the logic underlying Appellants' assertion that the PRO335 polypeptides would be useful as an immunostimulant is not inconsistent with the general knowledge in the art, and would be considered credible by a person skilled in the art. Further, Appellants respectfully submit that the Examiner's comments fail to support a *prima facie* case of lack of utility.

Accordingly, Appellants believe the rejections of Claims 39-47 and 49-51 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, to be improper, and respectfully request withdrawal of these rejections.

**ISSUE II: The Data Generated in the MLR Assay Satisfies the Enablement Requirement of 35 U.S.C. § 112, First Paragraph for Claims 39-47, 49-51**

In this regard, Appellants refer to the arguments and information presented above in response to the issue of utility, and those arguments are incorporated by reference herein. Appellants submit that, as discussed above, the MLR assay demonstrates utility for the PRO335 polypeptide for the treatment of conditions where the stimulation of lymphocyte proliferation would be desirable, including viral infections such as HIV and Epstein-Barr, and cancers such as melanoma. The present claims recite polypeptides that induce an inflammatory response. Support for this recitation is found in Example 74 which describes the MLR assay in which PRO335 polypeptides is an immunostimulant. Based on such a utility, one of skill in the art would know exactly how to use the claimed polypeptide PRO335, for the treatment of conditions where enhancement of an immune response is beneficial, without any undue experimentation.

Appellants also note that the claimed variants all share the functional recitation that "wherein said polypeptide is an immunostimulant." Example 74 of the present application provides detailed protocols for the MLR assay, including the extensive step-by-step guidance from Current Protocols in Immunology, which is explicitly incorporated into the specification by reference. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO335 polypeptide is capable of stimulating proliferation of T-lymphocytes. Appellants claim only polypeptides which meet both recitations of the claims, structural and

functional. So, the breadth of the claims are clearly defined by both the structural and functional recitations.

As indicated above, the specification provides detailed step-by-step guidance as to how to identify and make variant PRO335 polypeptides. The specification further describes methods for the determination of percent identity between two amino acid sequences (see for example, page 67, line 34 onwards to page 69). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 113, line 31, to page 115, line 8). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 114). Accordingly, one of skill in the art could identify and test the polypeptide to determine whether it is capable of being an immunostimulant by the methods set forth in Example 74; i.e., whether a variant PRO335 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods of preparing the PRO polypeptides (see page 115, line 10, to page 375, line 9).

As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-charge cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff. sub nom., *Massachusetts Institute of Technology v A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. §2164.01. A considerable amount of experimentation is permissible, if it is merely routine.

In view of the above, Appellants submit that a valid case for enablement has been made and would be considered credible by a person of ordinary skill in the art. Accordingly, Appellants believe the rejections of Claims 39-47 and 49-51 under 35 U.S.C. §112, first paragraph, to be improper, and respectfully request withdrawal of these rejections.

**ISSUE III: Claims 39-43, 50 and 51 satisfy the written description requirement of 35 U.S.C. §112, First Paragraph**

Claims 39-43, 50 and 51 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

In particular, the Examiner has asserted that "the claims do not require that the polynucleotide or encoded polypeptide possess a specific function associated with PRO335, only that the polypeptide encoded by said polynucleotide be immunostimulant. All polypeptides can be considered immunostimulants" (Page 16 of Final Office action). Appellants respectfully disagree.

**A. The Legal Test for Written Description**

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."<sup>25,26</sup> The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.<sup>27</sup> The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.<sup>28, 29</sup>

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<sup>25</sup> *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

<sup>26</sup> See also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

<sup>27</sup> See e.g., *Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

<sup>28</sup> *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

<sup>29</sup> See also M.P.E.P. §2163 II(A).

In *Environmental Designs, Ltd. v. Union Oil Co.*<sup>30</sup>, the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field."<sup>31</sup> Further, the "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."<sup>32, 33</sup>

**B. The Disclosure Provides Sufficient Written Description for the Claimed Invention**

Appellants respectfully submit that the instant specification evidences the actual reduction to practice of the amino acid sequence of SEQ ID NO: 290. Appellants also submit that they have clearly asserted that the polypeptide of SEQ ID NO: 290 shows a positive reaction in the MLR assay, and therefore would be considered by one skilled in the art as an immunostimulant, which is a specific function, due to this positive hit in the assay, which the Examiner himself has acknowledged. Any polypeptide would therefore NOT be considered an immunostimulant. Appellants have made their assertion for utility based on evidence.

Further, polypeptides having at least 80%-99% identity to SEQ ID NO: 290, which also show a positive hit in the MLR assay as immunostimulants are the only variant polypeptides encompassed in Claims 39-43. Polypeptides which have identity to SEQ ID NO: 290, but do not show an immunostimulant activity in the MLR are not encompassed. Appellants submit that the specification provides ample written support for determining percent sequence identity between

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<sup>30</sup> 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

<sup>31</sup> See also M.P.E.P. §2141.03.

<sup>32</sup> *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

<sup>33</sup> See also M.P.E.P. §2141.03.

two amino acid sequences (See pages 67-70, line 67 onwards). PRO polypeptide variants (independent claims 39-43) are clearly described in the specification at, for example, page 57, lines 2-14 and page 112, line 37 onwards, while identities to PRO polypeptide are described in the specification at, for example, page 67, line 34 onwards to page 69.

In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 44 and Table 6). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6). Accordingly, one of skill in the art could identify whether a variant PRO sequence that falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making the amino acid sequences (see page 376, line 9) and methods of preparing the PRO polypeptides (see Example 140-143). Further, the preparation of chimeric PRO polypeptides (Independent Claim 50 and claim 51), including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin, is set forth in the specification at page 74, lines 23 to page 75, line 5. Examples 53-56, pages 192-199, describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells. Therefore one skilled in the art would know that Applicants had possession of variant polypeptides of SEQ ID NO: 290.

Appellants further submit that the specification provides ample written support for the MLR assay to test the immunostimulant activity of these variant polypeptides, as described in Example 74. Example 74 of the present application provides step-by-step guidelines and by following this disclosure, one skilled in the art would know that it is easy to test whether a variant PRO335 protein is an immunostimulant in the MLR assay.

Thus, the genus of polypeptides with at least 80-99% sequence identity to SEQ ID NO: 290, which possess the functional property of being an immunostimulant would meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description. Accordingly, one skilled in the art would have known that Appellants had knowledge and possessed the claimed polypeptides with 80-99% sequence identity to SEQ ID NO: 290 which possess immunostimulant properties as determined in the MLR assay. The recited property of

immunostimulation adds to the characterization of the claimed polypeptide sequences in a manner that one of skill in the art could readily assess and understand.

For the above reasons, the specification provides adequate written description for polypeptides having at least 80% -99% identity to SEQ ID NO: 290, wherein the polypeptide is an immunostimulant in the MLR assay. Accordingly, Appellants respectfully request reconsideration and reversal of the written description rejection of Claims 39-43, 50 and 51 under 35 U.S.C. §112, first paragraph.

### **CONCLUSION**

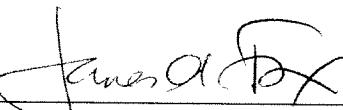
For the reasons given above, Appellants submit that the MLR assay, as disclosed in Example 74 of the specification sufficiently enables the instant invention. Therefore, Claims 39-47 and 49-51 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph. Accordingly, reversal of all the rejections of Claims 39-47 and 49-51 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-1618 P2C46**).

Respectfully submitted,

Date: December 3, 2007

By:



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## 8. **CLAIMS APPENDIX**

### **Claims on Appeal**

39. An isolated polypeptide comprising an amino acid sequence having at least 80% sequence identity to:

- (a) the amino acid sequence of the polypeptide of SEQ ID NO: 290;
- (b) the amino acid sequence of the polypeptide of SEQ ID NO: 290, lacking its associated signal peptide;
- (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 290; or
- (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,  
wherein said polypeptide is an immunostimulant.

40. An isolated polypeptide comprising an amino acid sequence having at least 85% sequence identity to:

- (a) the amino acid sequence of the polypeptide of SEQ ID NO: 290;
- (b) the amino acid sequence of the polypeptide of SEQ ID NO: 290, lacking its associated signal peptide;
- (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 290; or
- (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927,  
wherein said polypeptide is an immunostimulant.

41. An isolated polypeptide comprising an amino acid sequence having at least 90% sequence identity to:

- (a) the amino acid sequence of the polypeptide of SEQ ID NO: 290;
- (b) the amino acid sequence of the polypeptide of SEQ ID NO: 290, lacking its associated signal peptide;

- (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 290; or
- (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927, wherein said polypeptide is an immunostimulant.

42. An isolated polypeptide comprising an amino acid sequence having at least 95% sequence identity to:

- (a) the amino acid sequence of the polypeptide of SEQ ID NO: 290;
- (b) the amino acid sequence of the polypeptide of SEQ ID NO: 290, lacking its associated signal peptide;
- (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 290; or
- (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927, wherein said polypeptide is an immunostimulant.

43. An isolated polypeptide comprising an amino acid sequence having at least 99% sequence identity to:

- (a) the amino acid sequence of the polypeptide of SEQ ID NO: 290;
- (b) the amino acid sequence of the polypeptide of SEQ ID NO: 290, lacking its associated signal peptide;
- (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 290; or
- (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927, wherein said polypeptide is an immunostimulant.

44. An isolated polypeptide comprising:

- (a) the amino acid sequence of the polypeptide of SEQ ID NO: 290;

- (b) the amino acid sequence of the polypeptide of SEQ ID NO: 290, lacking its associated signal peptide;
- (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 290; or
- (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927.

45. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 290.

46. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 290, lacking its associated signal peptide.

47. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 290.

49. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209927.

50. A chimeric polypeptide comprising a polypeptide according to Claim 39 fused to a heterologous polypeptide.

51. The chimeric polypeptide of Claim 50, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.

## 9. EVIDENCE APPENDIX

1. Declaration of Sherman Fong, Ph.D. under 35 C.F.R 1.132, with attached Exhibits A-E:

- A. Current Protocols in Immunology, Vol. 1, Richard Coico, Series Ed., John Wiley & Sons, Inc., 1991, Unit 3.12.
- B. Steinman, R.M., "The dendritic cell advantage: New focus for immune-based therapies," *Drug News Perspect.* **13**:581-586 (2000).
- C. Gubler, U. et al., "Coexpression of two distinct genes is required to generate secreted bioactive cytotoxic lymphocyte maturation factor," *Proc. Natl. Acad. Sci. USA* **88**:4143-4147 (1991).
- D. Peterson, A.C. et al., "Immunization with melan-A peptide-pulsed peripheral blood mononuclear cells plus recombinant human interleukin-12 induces clinical activity and T-cell responses in advanced melanoma," *J. Clin. Oncol.* **21**:2342-2348 (2003).
- E. Thurner, B. et al., "Vaccination with Mage-3A1 peptide-pulsed mature, monocyte-derived dendritic cells expands specific cytotoxic T-cells and induces regression of some metastases in advanced stage IV melanoma," *J. Exp. Med.* **190**:1669-1678 (1999).

Item 1 was submitted with Appellants' Response filed October 25, 2004, and noted as considered by the Examiner on December 23, 2004.

**10. RELATED PROCEEDINGS APPENDIX**

None - no decision rendered by a Court or the Board in any related proceedings identified above.

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